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Published in:
Journal of Molecular and Cellular Cardiology

DOI:
[10.1016/j.yjmcc.2017.03.007](https://doi.org/10.1016/j.yjmcc.2017.03.007)

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Recommended citation(APA):
Headrick, J. P., Peart, J. N., Budiono, B. P., Shum, D. H. K., Neumann, D. L., & Stapelberg, N. J. C. (2017). The heartbreak of depression: 'Psycho-cardiac' coupling in myocardial infarction. *Journal of Molecular and Cellular Cardiology*, 106, 14-28. <https://doi.org/10.1016/j.yjmcc.2017.03.007>

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The heartbreak of depression: ‘Psycho-cardiac’ coupling in myocardial infarction

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Short Title: Depression and Myocardial Infarction

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ABSTRACT

Ample evidence identifies strong links between major depressive disorder (MDD) and both risk of ischemic or coronary heart disease (CHD) and resultant morbidity and mortality. The molecular mechanistic bases of these linkages are poorly defined. Systemic factors linked to MDD, including vascular dysfunction, atherosclerosis, obesity and diabetes, together with associated behavioural changes, all elevate CHD risk. Nonetheless, experimental evidence indicates the myocardium is also directly modified in depression, independently of these factors, impairing infarct tolerance and cardioprotection. It may be that MDD effectively breaks the heart's intrinsic defense mechanisms. Four extrinsic processes are implicated in this psycho-cardiac coupling, presenting potential targets for therapeutic intervention if causally involved: sympathetic over-activity *vs.* vagal under-activity, together with hypothalamic-pituitary-adrenal (HPA) axis and immuno-inflammatory dysfunctions. However, direct evidence of their involvement remains limited, and whether targeting these upstream mediators is effective (or practical) in limiting the cardiac consequences of MDD is unknown. Detailing *myocardial* phenotype in MDD can also inform approaches to cardioprotection, yet cardiac molecular changes are similarly ill defined. Studies support myocardial sensitization to ischemic insult in models of MDD, including worsened oxidative and nitrosative damage, apoptosis (with altered Bcl-2 family expression) and infarction. Moreover, depression may de-sensitize hearts to protective conditioning stimuli. The mechanistic underpinnings of these changes await delineation. Such information not only advances our fundamental understanding of psychological determinants of health, but also better informs management of the cardiac consequences of MDD and implementing cardioprotection in this cohort.

Keywords: Cardioprotection; Chronic Stress; Major Depressive Disorder; Ischemic Heart Disease; Myocardial Infarction

1. Introduction

Major depressive disorder (MDD) shares a reciprocal relationship with coronary heart disease (CHD) (reviewed in [1-3]). This behavioral disorder places healthy individuals at increased risk of CHD [4-7], is strongly linked to CHD in those with or without existing cardiac disease [6,8-10], is an independent risk factor for cardiovascular mortality and morbidity [11-13], and is more prevalent in those who have suffered AMI [12,14]. As a CHD risk factor, MDD exerts an impact similar to conventional determinants (eg. smoking, elevated cholesterol, hypertension, diabetes) [15,16], and increases the risk of recurrent cardiac events and death in those with CHD by up to 4-fold [11,17,18]. The magnitude of CHD risk is also related to the severity of MDD, ranging from a 2-fold increase to up to 5-fold with more severe depression [7]. Depression thus appears as powerful a determinant of CHD risk and outcomes as more traditional risk factors, and its occurrence is significant: recent analyses indicate a lifetime prevalence of ~16% in the US [19], with varying estimates from other populations (and diagnostic criteria), for example ~11% in Canada [20], 4-7% in Singapore [21], 12% in a Scottish cohort [22], 18% in urban Ethiopians [23], and 5% in rural-to-urban Chinese workers [24]. Whether overall incidence is on the rise is questionable, with a perceived growing epidemic of MDD and anxiety disorders potentially reflecting population growth, among other factors [25]. Whether more extensive 'sub-threshold' depression influences CHD risk and outcomes is also unclear.

As opposed to most major CHD risk factors, the biological mechanisms linking depressive disorders and heart disease remain to be detailed. From a holistic perspective [reviewed in 2,26], depressive and chronic heart disorders share the same physiological network of mechanisms (thus risk factors). This Psycho-Immune-Neuroendocrine (PINE) network is predicated on key regulatory systems [26], including the autonomic nervous, immune and endocrine systems, and components of the central nervous system (Figs. 1 & 2). Perturbation of the regulatory PINE network may predispose an individual to both MDD and CHD, with onset of either disease (and manifestation of

one ahead of the other) influenced by hereditary and environmental factors [26] (Fig. 1).

Highlighted in Fig. 1, there is a high degree of bidirectional interconnectedness between CHD and MDD – common mechanistic elements are implicated in both scenarios, and pathologic outcomes of each exert positive feedbacks on the other. For example, MDD may promote cardiac dysfunction via intermediate pathological and physiological mechanisms: behavioral changes with MDD contribute to inactivity, in turn promoting obesity, dyslipidemia, type 2 diabetes and hypertension, while associated social isolation additionally worsens CHD risk and mortality. There is also evidence that disruption of the PINE network can physiologically promote risk of dyslipidemia, type 2 diabetes and hypertension, and thus CHD [26]. The same intermediary pathologies can equally contribute to MDD.

Although now a well-recognized and clinically important manifestation of psycho-cardiac coupling, and while the PINE network model provides a framework for understanding depression-dependent changes in CHD risk and outcomes [26], relatively few studies have investigated the molecular mechanistic basis of these interactions. In particular, *how the heart itself is intrinsically modified by depression remains to be fully detailed*. Certainly, co-morbidities associated with or promoted by MDD, including obesity, diabetes and aging, are known to negatively impact myocardial stress-resistance and cardioprotection [27-30]. However, experimental evidence reveals that chronic stress and MDD *directly impair myocardial capacity to withstand injury/infarction independently of these systemic factors*. This review focuses on these direct myocardial impacts of depression, specifically the heart's capacity to withstand damage with infarction and respond to protective intervention. Not only contributing to worsened CHD risk and outcomes, depression may simultaneously render the heart resistant to cardioprotective interventions. While Tako-Tsubo cardiomyopathy exemplifies the notion of a 'broken heart', evidence suggests depression may effectively break the heart's intrinsic defense mechanisms, thus ability to withstand cellular injury and death. Beyond accumulating epidemiological evidence, and development of frameworks with

which to test and unravel these interactions [2,26] (Fig. 1), the molecular bases of these myocardial changes await more detailed investigation (Fig. 2).

2. Impacts of depression on myocardial infarction

2.1 Pre-ischemic depression

It is only relatively recently that studies have examined the detrimental impacts of stress and MDD on the heart's response to ischemic insult or infarction. Data generated in the landmark Whitehall study revealed strong relationships between social stress and metabolic and cardiovascular health outcomes [31-33]. In terms of those at risk of AMI, the prevalence of depression is significant with approximately 1-in-5 patients referred for diagnostic catheterization and angiography suffering pre-existing MDD [8,34], confirming significant prevalence of the disorder in those at risk of AMI. Early investigations revealed that depression impairs heart rate variability and autonomic control in humans [35], and that chronic stress (inducing depressive symptoms) increases heart rate, sympathetic tone, and cardiovascular reactivity to stress in animals [36,37], suggesting enhanced cardiac vulnerability to arrhythmia and injury. Further investigations over the last 3 decades have largely relied on chronic stress models (*eg.* subjecting animals to physical restraint, social isolation, predation stress, forced swimming, environmental instability, and randomized series of such stressors), which exhibit symptoms of depression that may include anhedonia and decreases in sexual drive, aggression, investigative behavior and locomotion, together with circadian disruption, disordered sleep and weight loss [38,39] (models discussed below in section 4). These studies identify both ultrastructural disruption in otherwise healthy hearts [40,41] and substantial changes in myocardial injury responses [40,42-47]. However, they have not yet developed a mechanistic understanding of these cardiac outcomes. Most research to date has focused on key end-points, including cell death, infarction, arrhythmogenesis and stunning, with few delving into underlying molecular mechanisms.

Scheuer and Mifflin showed that experimental infarction in rats is significantly worsened by daily restraint stress [42]. These investigators had previously identified worsened infarction in response to chronically elevated corticosterone [43]. Subsequent work indicates that chronic emotional stress exaggerates infarction in rats in association with increases in markers of oxidative and nitrosative damage [44]. Ravingerova *et al.* found chronic stress also increases contractile dysfunction and risk of post-ischemic arrhythmias in normotensive rats, though stress somewhat paradoxically improved these parameters in hypertensive animals [45]. While emulating post-traumatic stress disorder (PTSD), a more recent study in a psychosocial predator-based animal model reports increases in contractile dysfunction and myocardial death following ischemia, though specifically in males and not females [46]. Delving into mechanistic elements, Rakhshan *et al.* found that chronic physical or psychological stress worsened myocardial damage during infarction, and that this effect was eliminated by chemical sympathectomy (without influencing corticosterone levels) [47]. While not assessing infarction per se, Xinxing *et al.* report an association between myocardial injury and shifts in adrenaline, noradrenaline, corticosterone and 5-HT in a rat model of chronic stress [40]. There is thus some support for sympathetic over-activity and HPA dysfunction in myocardial stress intolerance in depressive disorders, though the identities and roles of neurohumoral factors involved await confirmation (Fig. 2).

There is also relatively little information available regarding the myocardial molecular changes that underpin these reductions in ischemic tolerance, with data essentially limited to damage markers and expression of pro- and anti-apoptotic Bcl-2 family proteins (Fig. 2). An analysis of cardiac and nervous responses reveals induction of Bax and repression of Bcl-xl transcripts in a rodent model of depression, potentially predisposing to apoptosis [48]. Subsequent investigations from this group confirm shifts in both transcript and protein for apoptotic regulators, including increased myocardial Bax, Bcl-2 and Bax/Bcl-2 ratio without changes in caspase-3 in rodent models of depression either prior to [49] or following [50] infarction. This may evidence

differential activation of caspase-3 independent death pathways with depression: Bax and Bcl2 not only modulate caspase-3 dependent apoptosis, but influence mitochondrial respiration, membrane permeability, cytochrome *c* release, and caspase-3 independent death. How these proteomic and cell death responses arise remains to be determined, though reported elevations in oxidative and nitrosative damage [44] will certainly promote apoptosis and oncosis. Nonetheless, the bases of the latter molecular damage outcomes are also unknown – are processes of reactive oxygen or nitrogen species generation dysregulated, and/or are anti-oxidant and molecular detoxification and repair mechanisms impaired with depression? There is preliminary evidence myocardial anti-oxidants levels are suppressed [44] and injurious toll-like receptor 4 and NFkB signaling up-regulated [41] with chronic stress, whereas cardioprotective NOS and Akt signaling are only modified by chronic stress (crowding) in the hearts of hypertensive and not normotensive rats [45,51]. Further work examining shifts in pro-survival vs. pro-injury signaling pathways across a broader range of models may clarify the basis of intrinsically impaired infarct tolerance in depression.

Other unknowns include the impacts of differing types and durations of stress. For example, while several models of chronic stress detrimentally influence myocardial infarct tolerance, crowding stress reportedly fails to modify infarction in hypertensive rats [51], while acute forms of stress can be cardioprotective. The latter response, a form of hormesis, is exemplified in the broadly conserved pre-conditioning phenomenon - transient ischemia induces powerful protection against subsequent prolonged insult. This contrasts the generally detrimental effects of chronic psychological stress on myocardial phenotype [52]. Both acute and chronic stressors may influence intrinsic myocardial defense mechanisms: chronic metabolic disorders and aging dysregulate survival kinase signaling engaged by acute stressors, resulting in impaired infarct tolerance [53,54]. Physical stress (*eg.* wheel-running in naïve mice) induces cardioprotection via the same kinase signaling [55], and our recent unpublished findings suggest that psychological effects of environmental enrichment (placement of a locked running wheel in cages) may similarly boost

infarct tolerance in caged mice, coupled with phospho-regulation of the same survival and stress kinases (see preliminary data in Fig. 3). These intriguing observations of acute protection via simple environmental enrichment warrant further investigation, highlighting the importance of psychological state in dictating myocardial phenotype and also raising questions regarding behavioral status in ‘control’ caged rodents. Finally, it is relevant to note there is evidence that the impacts of differing types of stress may be sex-dependent, with a model of PTSD selectively exaggerating post-ischemic myocardial damage and dysfunction in males only [46], while in contrast other stress (eg. crowding, sleep deprivation) worsens ischemic outcomes in females and not males [51,56].

From a cellular perspective, depression or chronic stress appears to impact all major cardiovascular elements. Studies to date support exaggerated cardiomyocyte apoptosis [40,49] and hypertrophy [57-59], together with myocyte abnormalities that include edema, myofibrillar damage and changes to mitochondria, nuclei and sarcoplasmic reticulum [40,41]. Myocyte contractile properties are also reportedly impaired, in association with depression of Ca^{2+} levels [59]. Exaggerated myocardial fibrosis, with increased transcripts for collagens, connective tissue growth factor and transforming growth factor- β 1 [57-59], implicate shifts in cardiac fibroblast phenotype/function. Coronary vascular function is also modified, with evidence of impaired coronary perfusion [45], while cardiac endothelial cells may also degenerate [41]. Chronic stress can also induce vascular stiffening [60], together with potentially adaptive NO generation and relaxation [61,62], though these outcomes have not been assessed specifically in coronary vessels. Thrombotic processes are also dysregulated, with evidence for involvement of circulating tissue factor (not vascular tissue factor, or platelet function) [63], although others report enhanced platelet aggregation [64]. Inflammatory and immune function is a key implicated element in the cardiovascular sequelae of MDD, and there is evidence for increased inflammatory cell infiltration and pro-inflammatory signaling in hearts of chronically stressed animals [41,58]. It thus appears all

major cellular elements of the heart, including myocytes, fibroblasts, endothelium and coronary vascular cells may be impacted in depression, together with invading or resident inflammatory/immune cells, and potentially platelets.

2.2 Post-Ischemic Depression

The occurrence of MDD after acute myocardial infarction (AMI) is well established, and is associated with both worsened quality of life [65] and higher mortality and rehospitalization [11,66, 67]. Up to 25% of patients suffer from depression post AMI, which is 2-4 times higher than the general population [8,34,68,69]. Though less well studied than the negative impacts of pre-existing depression, depression induced after AMI also appears to exaggerate cardiac apoptotic signaling and death [50] and tissue remodeling [70]. On the other hand, a recent study of post-infarction housing stress in rats found no significant effects on subsequent progression of heart failure [71]. Whether myocardial mechanisms underlying the effects of pre- vs. post-infarct depression are similar remains to be addressed, though Wang and colleagues find evidence of altered expression of apoptosis proteins in both scenarios [49,50].

3. Potential mediators of myocardial infarct intolerance in depression

There are 4 inter-related regulatory systems perturbed in MDD that plausibly give rise to myocardial intolerance to infarction (Figs. 1 & 2): sympathetic over-activity, vagal dysfunction, HPA axis abnormalities, and shifts in immune function and inflammation [2,26]. There is limited experimental support for involvement of the former neurohumoral mediators, while roles of immune and inflammatory processes have yet to be directly tested. The mechanistic roles of these 4 regulatory systems thus require more detailed investigation.

3.1 Sympathetic over-activity

The sympathetic nervous system is an important determinant of cardiovascular disease progression [72] and pathogenesis of AMI [73,74]. Individuals suffering depression exhibit increased sympathetic activity [74,75], including specifically elevated cardiac sympathetic tone [76]. This is also evidenced in reduced heart rate variability in psychological disorders including MDD [77-79]. Such autonomic dysfunction has been linked to increased risk of heart disease [80] and heart disease mortality and morbidity in MDD [35,81]. At a cellular level chronic sympathetic activation can increase oxidative stress and dysregulate apoptotic pathways to worsen myocardial injury [82]. Sustained release or sudden spikes in catecholamine levels also increase risk of cardiac complications such as arrhythmias and sudden cardiac death. Modulation of autonomic nervous activity has been shown to reduce myocardial ischemia-reperfusion injury [83-86], and β -blockade has been a mainstay in management of patients with CHD/AMI.

The myocardial effects of sympathetic over-activity are certainly consistent with involvement in the negative consequences of MDD (Fig. 2). Increased β -adrenergic receptor activity promotes both apoptosis and oncosis [87-90], with pro-death effects potentially involving NADPH oxidase activity [91,92], nitric oxide generation and nitrosative stress [93,94], and modulation of Bcl-2 protein expression profiles [90,95]. Oxidative stress with noradrenaline has also been linked to epigenetic repression of protective PKC ϵ (via NADPH oxidase-1 dependent oxidative stress) [96]. Additionally, increased β -adrenergic receptor activity enhances apoptotic death in response to immuno-inflammatory activation [95], in association with altered stress kinase signaling and Bcl-2 expression. These putative mechanisms are consistent with the elevations in myocardial oxidative and nitrosative stress [44], shifts in Bcl-2 proteins and execution of apoptosis [47-49], and inflammatory responses [41,58] observed in animal models of depression. Cardiac pathologies relevant to risk of and outcomes from AMI have also been linked to β -adrenergic receptor activity in models of chronic stress, including hypertrophy, fibrosis, diastolic dysfunction

and oxidative stress [58].

Although widely assumed, reflecting pro-infarct effects of sympathetic activity in other settings, the involvement of sympathetic over-activity in infarct intolerance in MDD has yet to be thoroughly tested. Furthermore, whether the degree and pattern of sympathetic activation in animal models of depression reflect changes and roles in human MDD is not at all clear. The recent report of Rakhshan *et al.* suggests reduced infarct tolerance in a rat model of chronic stress is blocked by chemical sympathectomy [47], consistent with involvement of sympathetic over-activity. Variable effects of sympathectomy on infarct tolerance [97-99] nonetheless raise questions regarding selectivity and the mechanistic basis of sympathectomy outcomes. That said, studies also confirm elevations in circulating noradrenaline and adrenaline in MDD [74-76], and Xinxing *et al.* recently report *in vitro* cytotoxicity in otherwise healthy cells subjected to changes in noradrenaline, corticosterone and 5-HT that mimic those in a rat model of chronic stress [40]. However, the involvement of these factors in stress-dependent myocardial changes *in vivo* has yet to be directly tested. For example, a reduction in 5-HT with chronic stress [40] might also promote cell survival given recent evidence of 5-HT receptor involvement in cardiac apoptosis and remodeling following adrenergic activation [100].

It is also important to note that effects of cardiac nerves on ischemic injury are complex, and adrenergic receptor sub-types exert distinct effects on myocyte survival vs. death. Regional ischemia activates the autonomic nervous system, reducing electrical stability and promoting arrhythmias, modifying cardiac O₂ supply/demand and worsening myocardial injury. However, disrupting extra-cardiac nervous system input can exert either protective [97,98,101] or injurious effects [102,103]. Indeed, it has been suggested that absence of cardiac nerve activity may impair cardiac functional recovery [104]. In terms of cardioprotection, the second (delayed) but not first (acute) window of protection with pre-conditioning may require cardiac nerve activity [105]. Others report that surgical denervation does not eliminate pre-conditioning in dogs, yet significantly

reduces infarction alone [101]. The cardiac α - and β -adrenergic receptor sub-types activated by noradrenaline and adrenaline also exert opposing effects on stress responses and cell death. Activation of β -adrenergic receptors can protect against or promote cell death [90], with β_1 activity contributing to both cardiac apoptosis [90,95,106] and cardioprotection via ischemic preconditioning [106-109], while β_2 receptor activity may contribute to myocyte survival, ischemic tolerance and preconditioning responses [90,110,111]. The α_1 adrenergic receptors also exert opposing effects, with the higher affinity α_{1A} receptor promoting myocyte survival and ischemic tolerance [112-114], contributing to delayed cardioprotection [115], and improved angiogenesis [116], remodeling and survival [117] post-infarction. The survival effects of α_{1A} receptor activity may involve modulation of Bcl-2 proteins implicated in the pro-apoptotic response to β -adrenergic receptor activity, providing a counterbalance to limit apoptosis with sympathetic over-activity. Conversely the lower affinity α_{1B} -adrenergic receptor may promote hypertrophy and contractile dysfunction [118], and as opposed to the longevity (and anti-cancer) effects of α_{1A} activity, appears to reduce lifespan [119]. Thus, sympathetic activation and HPA axis dysfunction may induce differential effects on cardiac death, remodeling processes and overall survival, governed by adrenergic receptor sub-type expression and activation patterns. These complexities, coupled with the limited analyses of sympathetic over-activity to date, indicate more direct and thorough assessment is needed to identify roles of sympathetic nervous and humoral signaling in reducing myocardial infarct tolerance in MDD (Fig. 2).

3.2 Vagal dysfunction

Major depressive disorder is associated with reduced vagal activity, with evidence of a causal relationship between vagal function and depression [3,120]. Importantly, vagal dysfunction is likely to impair myocardial infarct tolerance, and may also negate capacity to protect the heart of MDD patients via widely trialed pre-conditioning interventions (Fig. 1). Detailed below, vagal

stimulation and the primary vagal transmitter acetylcholine protect against cardiac and vascular injuries, and play an essential role in ischemic pre-conditioning responses (Fig. 2).

Early clinical studies identified the importance of autonomic function in mortality following AMI [121,122], with experimental studies establishing the role of vagal activity in limiting arrhythmogenesis and enhancing survival post-AMI [123-127]. Investigations subsequent to these analyses of electrical stability/arrhythmogenesis revealed that acetylcholine and muscarinic receptor agonists also protect mammalian myocardium from ischemic injury [128,129], initially implicating reactive oxygen species signaling and ATP-gated K^+ channel activity [130-133] together with nitric oxide [134].

Later studies established that vagal stimulation, confirmed to increase cardiac interstitial acetylcholine [135], also reduces ischemic damage and infarction [136-139], and improves post-infarct inflammation and remodeling [140]. The protective effects of vagal activity and acetylcholine are not limited to myocardial cells, extending to protection of coronary vascular cells [134] and reduction of peripheral vascular inflammation and injury [141] during infarction. Other work confirms essential involvement of vagal activity in cardioprotection via remote pre-conditioning [142,143], with evidence release of the protective factor (which induces protection via recruiting intrinsic cardiac ganglia) is dependent upon prior vagal activation [144].

Mechanistically, while initial studies focused on roles of reactive oxygen species, K_{ATP} channels and nitric oxide in the protection elicited by acetylcholine and muscarinic receptors, studies also support roles for improved Ca^{2+} handling [145,146], and the ‘cholinergic anti-inflammatory pathway’ (involving suppression of JAK-STAT and NF κ B signaling) appears key to the cardiac and vascular protection with vagal activity (Fig. 2). Acetylcholine modulates myocyte expression of inflammatory cytokines [147], and vagal stimulation reduces neutrophil invasion and inflammatory markers in post-ischemic myocardium [137], modifies TNF- α expression and differentially modulates protective *vs.* injurious TNF receptor sub-types[138,148], and inhibits

expression of injurious Il-17a during infarction [149].

Interestingly, more recent work in cultured cell models of hypoxia/reoxygenation injury supports beneficial effects of acetylcholine on autophagy [150], and mitochondrial biogenesis [151] and quality control via mitophagy [152]. Similarly, vagal nerve stimulation may limit myocardial injury by inhibiting mitochondrial dysfunction and associated apoptosis [139], though this study found protection was limited to intra-ischemic intervention while post-ischemic stimulation was ineffective. Other work supports vagal control of mitochondrial dynamics, likely promoting stress-tolerance and limiting cell death [153]. Inhibition of the mitochondrial unfolded protein response may additionally contribute to anti-apoptotic effects of acetylcholine, potentially via inhibition of mitochondrial oxidant generation [154]. Studies thus collectively reveal important roles for vagal activity in dynamic maintenance of mitochondrial phenotype and function. While neuronal autophagy appears dysregulated with depression, the effects of MDD or chronic psychological stress on cardiac fission, fusion and mitophagy await analysis.

Both muscarinic (M2, M3) receptors and nicotinic receptors may contribute to the protective effects of vagal activity and acetylcholine. Studies initially focused on muscarinic M2 receptors, with antagonism or knockdown confirming involvement in protection of cardiomyocytes [147,155]. Additionally, M3 agonism with choline is cardioprotective [146,156], and the M3 receptor is implicated in the anti-apoptotic effects of acetylcholine [154] and in vagally mediated protection [133]. Finally, nicotinic receptors may also participate, with the study of Calvillo *et al.* supporting involvement of the nicotinic pathway and inflammatory modulation in cardioprotection via vagal stimulation [137]. Activation of the $\alpha 7$ nACh receptor also substantially limits inflammation during myocardial ischemia-reperfusion [157], and may promote angiogenesis post-infarction [158] (Fig. 2).

Despite considerable evidence supporting cardiac protection via vagal activity in other settings, no study has yet demonstrated that reduced vagal activity underlies exaggerated

myocardial infarction in models of MDD. This is important if vagally targeted therapies were to be implemented. Clinically, vagal stimulation has been assessed in chronic heart failure, where it has been established as safe and efficacious [159-161]. Trials in myocardial infarction (or surgical ischemia) have yet to be undertaken. Among other unknowns, it is unclear whether detrimental impacts of sympathetic and vagal dysfunction on infarction and cardioprotective signaling are additive or potentially synergistic. It is thus unclear whether combined targeting of vagal and sympathetic pathways will be substantially more effective, practical or problematic, in terms of protecting against ischemic damage and infarction. We are unaware of studies assessing dual treatment via both parasympathetic agonism/nerve stimulation and sympathetic antagonism/nerve block. Although in a different setting, combined vagal stimulation and β -blockade has been shown to be more effective than either alone in preserving function in a model of chronic heart failure [162].

3.3 The HPA axis

The endocrine response to stress involves anterior hypothalamic release of corticotropin-releasing hormone, and pituitary secretion of adrenocorticotrophic hormone to stimulate adrenal cortex secretion of glucocorticoids such as cortisol [163]. Chronic stress results in over-secretion of glucocorticoids and downstream adrenal catecholamines [164]. Inflammatory dysfunction is an important element in MDD, and cytokines also stimulate the HPA axis, with IL-6 particularly important in axis activation during chronic stress [165]. Additionally, eicosanoids, platelet-activating factor and serotonin act as inflammatory mediators to stimulate the HPA axis [166]. Chronic activation of the HPA axis in depression may both directly and indirectly influence myocardial phenotype and stress-tolerance (Figs. 1 & 2).

Glucocorticoids exert direct cardiovascular effects, including positive inotropism and increased blood pressure and cardiac output [167]. They also sensitize the cardiovascular system to

catecholamines, and prolong the actions of catecholamines at neuromuscular junctions [163].

Coupled with sympathetic over-activation, HPA axis dysfunction may exaggerate the pro-injurious actions of catecholamines. In addition, cortisol inhibits insulin and promotes lipolysis, modifying substrate metabolism and elevating blood glucose. Chronic stress also induces insulin-resistance, further promoting hyperglycemia, with both hyperglycemia and insulin-resistance known to impair infarct tolerance and cardioprotective signaling [27-30,168,169]. Similarly, elevations in serum fatty acids, particularly saturated forms, may induce myocardial dysfunction and apoptotic death, while polyunsaturated fats are protective [170,171]. Whether cortisol-dependent inhibition might also limit the cardioprotective action of insulin [89,172] has not been tested.

Stimulation of the HPA axis reduces production of thyroid-stimulating hormone and conversion of thyroxine to triiodothyronine (Fig. 2), which can lead to sick euthyroid syndrome [173], associated with cardiac dysfunction under normoxic and post-ischemic conditions [174]. It is less clear whether infarction is sensitive to this imbalance [175], although sick euthyroid syndrome is associated with greater in-hospital and long-term mortality in AMI patients undergoing percutaneous intervention [176]. Gonadal steroid secretion is also reduced with HPA axis activation [163], with evidence maintenance of testosterone levels reduces major adverse cardiovascular events and death [177], while protective effects of estrogen are well established [178]. Finally, prolonged activation of the HPA axis also inhibits growth hormone secretion and IGF-1 [179], with the growth hormone/IGF-1 axis known to reduce CHD risk and protect myocardium against infarction [180,181]. This spectrum of neuroendocrine outcomes with HPA axis dysfunction may collectively contribute to stress intolerance and other myocardial changes. In turn, HPA axis dysfunction has been extensively demonstrated in MDD [26] and other mental illness such as anxiety disorders [182,183]. While links between MDD and myocardial damage can be postulated in terms of mechanisms of autonomic and HPA axis dysregulation, their individual roles and contributions have yet to be detailed. Changes in HPA hormones have potential to modify cell death

processes [40], yet no study has confirmed involvement of HPA dysfunction in the effects of MDD on myocardial infarct tolerance.

3.4 Immuno-inflammatory function

Depression increases pro-inflammatory cytokine production and levels of acute-phase proteins, chemokines and adhesion molecules [184-189] (Figs. 1 & 2). Pro-inflammatory cytokines (eg. IL-1, IL-6, TNF α) promote fatigue, somnolence and withdrawal from social activity [189-191]. Moreover, endotoxin induces anhedonia in rats, coupled with somnolence and reduced exploratory and social behavior and food intake [191], and in humans induces anxiety, depressed mood and impaired memory function [192]. These symptoms have been termed ‘sickness behavior’ [191-195], and mirror the neuro-vegetative features of MDD. Importantly, sickness behavior symptoms induced with pro-inflammatory cytokines are reversed with anti-depressant medication [190,196].

Stress-dependent modulation of the immune response and pro-inflammatory cytokines also increases infection susceptibility [197,198], and in humans chronic stress is associated with susceptibility to viral infection, delayed wound healing, and impaired antibody responses to vaccination [199,200]. These changes are influenced, in turn, by other elements of the integrated network of mechanisms that can result in MDD [26] (Fig. 1). For example, both vagal activity and the HPA axis impact immune function and inflammation, and corticosteroids impair humoral immunity and increase autoimmune inflammatory responses [201] (Figs. 1 and 2). Long-term elevations in cortisol with chronic stress can thus promote autoimmune responses while limiting capacity to fight infection. In addition, myocardial apoptosis with endotoxemia appears to be promoted by β -adrenergic receptor activity [95], suggesting potential synergism between sympathetic activity, immune and inflammatory function in MDD.

Pro-inflammatory cytokines are known to exaggerate myocardial damage during infarction, although effects are complex with evidence of protective actions of transient elevations in cytokines

including TNF α [202], together with roles in promoting post-infarct healing [203-205]. Immune function is also a critical determinant of infarct outcomes and cardioprotection [206-209]. While no studies have effectively confirmed mechanistic involvement of perturbed inflammation and immune function in the impacts of MDD or chronic stress on infarct tolerance, there is evidence for inflammatory cell infiltration, activation of inflammatory signaling, and toll-like receptor 4 and NF κ B dependent myocardial injury in models of chronic stress [41,58]. Chronic stress also increases macrophage infiltration and growth and vulnerability of atherosclerotic plaques, in association with exaggerated infarct occurrence and injury [210].

4. Animal models of depression and their use in studies of infarct tolerance

Modeling human disease in animals poses a major challenge in examining mechanisms governing myocardial phenotype in depression. Issues include the perennial complication of species-specific biology, and questions regarding the nature of behavioral pathologies induced in different models. Importantly, while no single model replicates the range of physiological, psychological and social components of human depression, specific animal models do manifest important elements of the disorder [211]. As outlined by Willner [39], the validity of animal models is determined by 3 characteristics: the model should replicate the symptoms of human depression (face validity); model symptoms should involve neurophysiologic mechanisms corresponding to those in humans (construct validity); and pharmacological or other interventions should appropriately influence behavioral outcomes (predictive validity). Of course, it is problematic to ascertain the true construct validity of any animal model while the neurophysiological mechanisms underpinning human depression remain poorly defined. Limitations or complications relevant to all such models include evidence of significant strain- [212-216], sex- [46,51,217,218] and age-dependent [219-222] outcomes and responses to anti-depressants.

As the diversity of animal models, their pros, cons and relevance to human depression have

been reviewed in detail previously [211,223-225], they are addressed here in brief. Animal models of depression may be generally divided according to the means of induction of depressive behavior:

i) exposure to acute or sub-chronic stress, including the despair-based forced swimming and tail suspension test models. However, there are questions regarding the validity of these models, and they tend to produce limited and short-lasting depressive-like symptoms. On the other hand, the learned helplessness model (discussed below) does generate longer lasting behavioral and cognitive changes and appears a more valid model within this sub-set.

ii) chronic exposure to multiple 'mild' stressors, inducing depressive-like symptoms including anhedonia, reduced activity and changes in appetite and weight. It is important to recognize, however, that the key behavioral indicator of depressive state in these models - anhedonia-like behavior - is not specific to depression, arising in some other behavioral disorders.

iii) modulation of select physiologic processes to manifest depressive symptoms and examine the molecular pathogenesis of depression (eg. modulating HPA axis or immune function). However, considerable heterogeneity in behavioral outcomes may arise in such models, and outcomes may also not be specific to depression.

iv) genetic models [226-228] or surgical manipulations (eg. olfactory bulbectomy [220]) to modify phenotype and behavior, again more relevant in investigating specific pathophysiological elements of depressive disorders.

The three models most widely applied in pre-clinical research in recent years are the chronic mild stress, forced swim test, and learned helplessness models [224]. The former is most commonly applied in studying myocardial stress responses and infarct tolerance. Analyses of myocardial outcomes across a broader range of models are warranted, including effects of the forced swim test and learned helplessness models on infarct incidence and tolerance.

Chronic mild stress. The chronic mild stress model of depression was initially developed over 35 years ago [229,230], and has been adapted by investigators in studying multiple aspects of

depression including cardiac infarct intolerance [44,48-50]. Greater validity and manifestation of long-lasting depressive symptomatology are advantages [39]. The model triggers antidepressant-sensitive anhedonia-like behavior (assessed from reduced sucrose consumption and preference) and other depressive characteristics (reduced exploratory behavior and grooming), together with shifts in neurotransmitter signaling. These behaviors are induced over a 3-9 wk induction period in which differing stressors are applied in random/semi-random order, limiting capacity to adapt. However, widely varying durations of stress across studies may lead to differing outcomes, with the impact(s) of stressor duration yet to be adequately examined. The model is considered superior to the learned helplessness and forced swim test models in terms of the time-course and specific symptoms of depression, and also effects of anti-depressants. Disadvantages are in part practical – the method is highly labor intensive, the variety and durations of stress raise ethical concerns and may limit ethics approval, and importantly the model can be difficult to establish, with considerable variations in outcome despite use of similar protocols [39]. Additionally, repeated stressors (despite randomization) have the potential to induce resilient phenotypes, complicating interpretation. Commonly incorporated within chronic mild stress models, both crowding [231-233] and restraint [234,235] are also employed as individual stressors. However, it is possible resilience/adaptation arises, limiting their applicability. Studies do support a greater capacity to trigger depressive symptoms with unpredictable forms of stress rather than restraint alone [236], and there is also some evidence crowding stress does not alter infarct tolerance [51]. Social isolation as a sole stress has also not been examined for effects on myocardial infarct tolerance, though has been incorporated with other stressors in studies of chronic mild stress [48-50].

Forced swim test. In this model rodents are forced to swim in a partially fluid-filled cylinder in order to survive an inescapable situation. A pre-test swim of ~15 min is thought to induce behavioral despair, and is followed 24 hrs later by a brief 5 min session. Instances and duration of immobility are used as primary indicators of behavioral despair. Although the forced swim test is

widely employed in studies of depression, this is largely a reflection of its simplicity, low cost and short experimental duration rather than model validity, which remains questionable [237,238]. Indeed, the short induction period contrasts patterns of depression development in humans. Moreover, variations in parameters such as number of training sessions, testing durations and equipment dimensions can significantly impact outcomes. Nonetheless, the practical aspects of the model render it popular in high-throughput screening of anti-depressant responses [239]. The model has not yet been applied in studying potential shifts in cardiac infarct tolerance.

Learned helplessness. The learned helplessness model is increasingly employed, though yet to be applied in studying effects on cardiovascular phenotype and stress tolerance. Helplessness is a central feature of clinical depression, and is inducible in animal models. Learned helplessness reflects a failure to control unpleasant stimuli, and subsequently avoid stressful events. Unavoidable electrical shocks are used to induce helplessness in rodents, leading to development of 'escape failure' - a negative coping strategy in which animals no longer avoid stress. The model induces depressive symptoms, including anxiety-like behavior, and decreased exploratory behavior, locomotion and body growth [240-243]. Nonetheless, it is important to note that inescapable stress in humans induces short-term depressive-like symptoms not characteristic of clinical depression. Moreover, from a practical perspective relatively little is known regarding impacts of protocol variations on behavioral and other outcomes. Despite these limitations, together with the complexity of the protocol, need for specialized equipment and application of electrical shocks, learned helplessness is arguably one of the more valid animal models of depression [244]. While not yet studied for impacts on cardiac stress responses and infarct tolerance, the direct and indirect effects of unavoidable electrical shock were recently studied by Rakhshan and colleagues [47].

4.1. Application in studies of cardiac ischemic tolerance

Changes in myocardial responses to ischemia-reperfusion have only been assessed in a sub-

set of these depression models. Inhibitory effects on ischemic tolerance have been demonstrated in models of chronic mild stress that include: 20 day administration of stressors (daylight/darkness exposure, overcrowding, isolation, new hierarchy, cage tilting, restriction of water or food) [44]; or 21 days of randomized stressors (confinement to a small cage, restraint, water deprivation, food deprivation, isolation, flashing light, forced cold water swimming, group-housing in a soiled cage) [48-50]. Scheuer *et al.* tested the effects of chronic (1-2 hrs/day for up to 14 days) restraint stress [42], while crowding stress was assessed by Ravingerova *et al.* (living space reduced from 480 cm²/rat to 200 cm²/rat for 8 wks) [45] and Ledvenyiova-Farkasova *et al.* (living space reduced from 200 to 70 cm²/100 g body mass for 2 weeks) [51]. Rakhshan *et al.* employed a model of daily electrical shocks (over a 1 hr period/day for 1 wk) or witnessing shocks in communal housing [47], mimicking in part elements of the learned helplessness model. As detailed above, these forms of chronic stress increase both infarction and contractile dysfunction [42,47], or selectively influence contractile recovery [45,51]. Infarct intolerance is also evident in stress models reflective of other disorders, including sleep deprivation [56] and a predator/stress model of PTSD [46]. Interestingly, 2 weeks of crowding stress studied by Ledvényiová-Farkašová and colleagues [51] failed to influence infarct tolerance in normotensive animals, though selectively reduced contractile recoveries in female hearts (association with reduced NOS activity). This contrasts outcomes in models of restraint stress [42], chronic mild stress [40,44,48-50] and physical and psychological stress [47], suggestive of a lesser cardiac impact of crowding. Although it has been noted that chronic stress can yield mixed results in terms of myocardial infarct tolerance [52], this may reflect differing cardiovascular responses to metabolic vs. psychologic stressors. For example, both short-term and chronic hypoxic stressors are cardioprotective [245], as are brief and chronic caloric limitation [246] or physical exercise [247]. However, in the case of chronic ‘forced’ exercise, attendant psychological stress may contribute to cardiac detriment that is resistant to metabolic modulation [248].

A key limitation in a number of these investigations is failure to undertake behavioral assessment to confirm depressive states prior to myocardial insult. The studies in which behavioral responses were validated prior to ischemic injury include those of chronic mild stress by Wang *et al.* [48-50] and Xingxing *et al.* [40], and the work of Rorabaugh and colleagues in a model of PTSD [46]. No behavioral outcomes were assessed in other studies of the cardiac impacts of chronic mild stress [44], or chronic physical or psychological [47], restraint [43] or crowding [45] stress. Studies of other negative cardiovascular consequences of stress also fail to adequately assess associated behavioral changes [58].

5. Relevance to clinical cardioprotection

Beyond reducing the risk and prevalence of CHD, a long-running and intractable challenge in cardiology has been the development of cardioprotective therapy to limit myocardial injury with AMI or ischemic surgery [28-30,249]. Early reperfusion remains the sole approach to salvage ischemic tissue, yet itself induces additional damage, and benefit remains variable and highly time-sensitive. There are few clinical scenarios in which outcome is so critically time-dependent: reperfusion is optimal within a 1.5-2 hr window that is rarely achieved in AMI - most Australians for example are reperfused >2.5 hrs from symptom onset, with less than 25% receiving 'timely' reperfusion [250]. Even optimally timed reperfusion yields highly variable outcomes [251]. As we and others argue [27-30], failure to clinically translate cardioprotection reflects in part failure to address the negative influences of aging, drugs and common co-morbid conditions (including atherosclerosis, obesity, diabetes, hypertension) on the myocardial defense mechanisms targeted by widely studied and trialed interventions. Though highly effective in young healthy hearts, many cardioprotective interventions appear less effective (if at all) in older hearts or in the presence of other co-morbid conditions. Depression is thus a key co-morbidity that has received even less attention than aging, obesity, diabetes or hypertension. Approximately 20% of CHD patients suffer

from MDD [8,34], while up to 25% of patients suffer depression post-infarction [252]. Thus, approaches to both acute protection against AMI and also later protection against delayed injury and remodeling may be significantly impacted.

The depressed CHD patient may pose a particularly problematic challenge. Protection via pre-conditioning may require cardiac nerve activity [105], although this remains contentious [101], and both vagal activity [142-144] and sympathetic signaling [106,107,253,254] have been implicated in ischemic pre- and post-conditioning responses. Thus, the sympathetic and vagal dysfunction potentially worsening infarct tolerance with depression may render these hearts less responsive to conditioning interventions. The effects of MDD and chronic stress on the expression and functionality of protective signaling pathways engaged by these stimuli, including the ‘reperfusion injury salvage kinase’ or RISK path [255], and the ‘survivor activating factor enhancement’ or SAFE path [202], are largely unstudied. To date only one investigation has directly tested the effects of depression on conditioning responses, supporting inhibition of ischemic post-conditioning in a rat model of chronic mild stress, potentially involving impaired post-ischemic activation of protein kinase B and STAT-3 [256]. Curiously, the study did not identify any impact of chronic mild stress on infarct size in non-preconditioned hearts, contrary to other reports of exaggerated cell death and infarction in similar models [40,44,48-50].

6. Myocardial effects of anti-depressants

Interactions between mood and cardiac phenotype are further evidenced by beneficial myocardial effects of anti-depressants [257], which can also improve AMI outcomes and CHD mortality [258]. However, it is important to highlight that to date no fully powered study has confirmed that anti-depressant (or psycho) therapy improves survival following AMI. Although consistent with the detrimental cardiac impacts of depression, interpretation of the above findings is complicated by pleiotropic cardioprotective effects of such agents [259,260]. Moreover, other

agents exhibiting cardioprotective actions also mediate anti-depressant effects (*eg.* resveratrol [261]), supporting a broad influence of cardiovascular health on depression. A detailed analysis of the cardioprotective effects of anti-depressants is needed, in particular identifying the molecular mechanisms of such effects, and whether these agents can act directly on the myocardium, independently of effects within the central nervous system.

7. Concluding remarks

In summary, studies to date indicate that models of depression worsen myocardial death and dysfunction following ischemia or infarction. However, there is a need to perform studies in a broader range of animal models (with behavioral outcomes confirmed), and the upstream mediators and molecular basis of myocardial changes remain to be detailed. In terms of neurohumoral mediators, there is some limited evidence for involvement of sympathetic over-activity [47], coupled with indirect evidence implicating catecholamines and 5-HT [40]. Further delineation of the roles of the major components of the PINE network - the autonomic nervous, immune and inflammatory systems, and the HPA axis - in inducing myocardial infarct intolerance with MDD is critical in understanding the reciprocal relationship between MDD and CHD. At the level of the myocardium itself, we also have a rather basic view of alterations in chronic stress models of MDD (or indeed MDD patients), with injury end-points primarily assessed to date. These studies support exaggerated oxidative and nitrosative damage [44], altered expression of Bcl-2 proteins and increased apoptosis and infarction [48-50], leaving the regulatory or signaling basis somewhat obscure: how are molecular oxidative and nitrosative damage exaggerated, Bcl-2 proteins and apoptosis pathways modified, and infarction worsened by MDD? Equally important - how does chronic stress or MDD influence the heart's intrinsic cytoprotective mechanisms and responsiveness to cardioprotective therapies. A single study indicates depression negates the ability of ischemic post-conditioning to limit infarction in rats [256], suggesting that depressive states may

be an additional factor in the inability of cardioprotective stimuli to limit infarction in those suffering CHD [29,30,249]. Identifying specific myocardial modifications underlying impaired infarct tolerance can facilitate development of approaches to improving cardiac phenotype and ischemic outcomes in this significant patient population.

Acknowledgements: There are no acknowledgements

Disclosures: None declared.

Funding: The work was supported by Griffith University and the Menzies Health Institute QLD.

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FIGURES

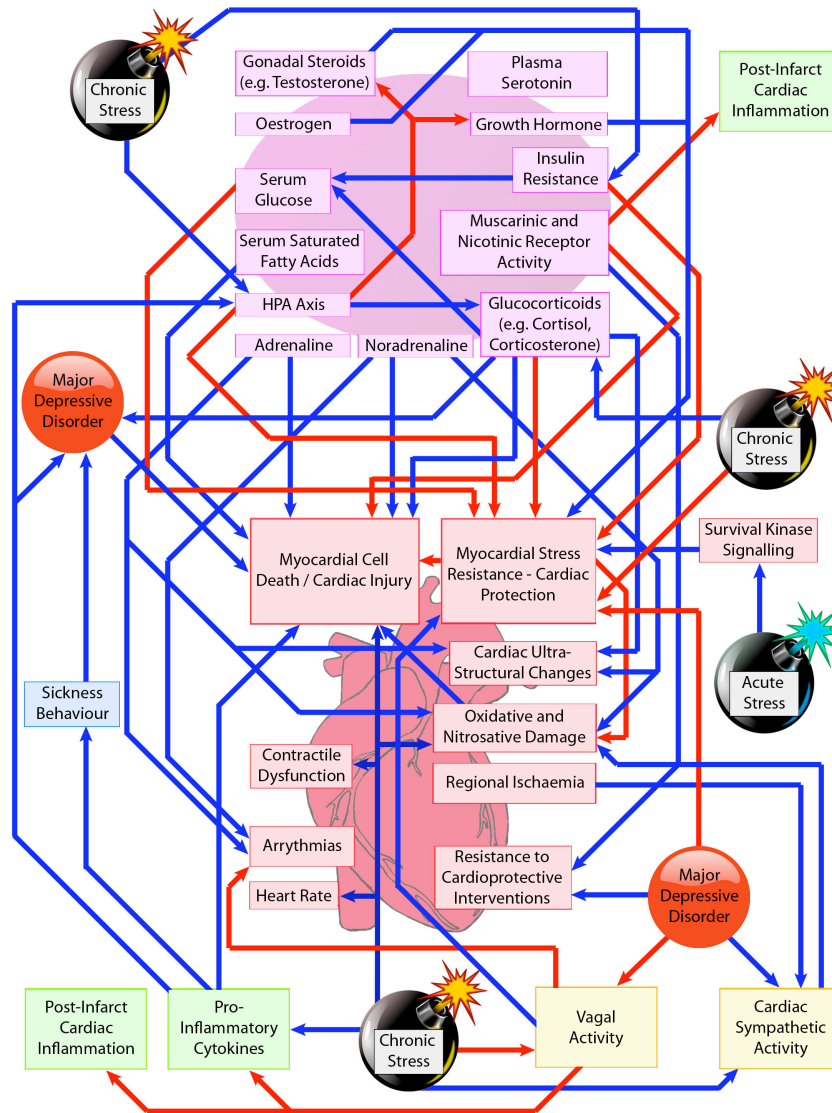
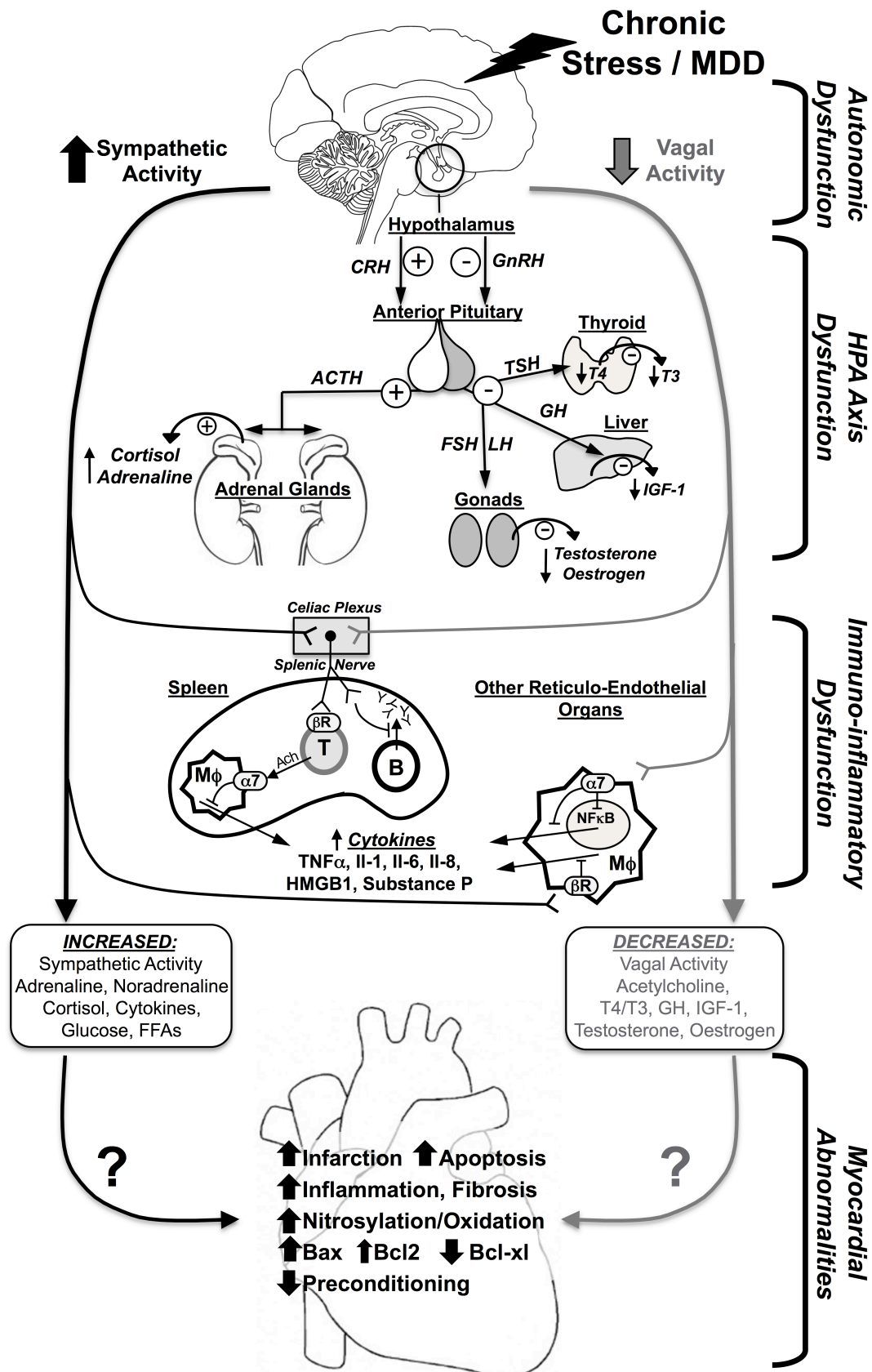


Fig. 1. Directional network map highlighting the pathways linking chronic stress and MDD to multiple mechanisms of cardiac pathology. Biological systems (boxes) which are nodes in the network are depicted in different colors (endocrine mechanisms, purple; autonomic activity, yellow; inflammatory mechanisms, green; mechanisms relating to both cardiac tissues and function, red). Arrows are colored according effects on target nodes (promotes = blue; inhibits = red).



Inputs potentially influencing cardiac phenotype are highlighted. Not shown are CNS feedbacks (eg. vagal/sensory afferents, HPA activation by cytokines/inflammation)

Fig. 2. Potential signaling governing myocardial stress phenotype in MDD. Within myocardium MDD/stress impairs infarct tolerance and cardioprotection, in association with

exaggerated nitrosative/oxidative damage, altered expression of apoptotic mediators and increased apoptosis. The basis of these direct myocardial changes remains unclear. MDD (and chronic stress models of MDD) are associated with sympathetic activation *vs.* vagal suppression, HPA axis dysfunction, inflammation and immunomodulation. The HPA axis dysfunction: elevates adrenal glucocorticoid (*eg.* cortisol) secretion via hypothalamic corticotropin release hormone (CRH) and anterior pituitary adrenocorticotrophic hormone (ACTH) release; suppresses gonadal hormone production (testosterone, estrogen) via reduced hypothalamic gonadotropin releasing hormone (GnRH) and pituitary gonadotropin (LS, FSH) secretion; and suppresses thyroid thyroxine (T4) and circulating triiodothyronine (T3) levels, and hepatic insulin-like growth factor-1 (IGF-1) release via reductions in pituitary thyroid-stimulating hormone (TSH) and growth hormone (GH) secretion, respectively. Vagal activity directly impacts the heart, and modifies stress responses/remodeling via the cholinergic anti-inflammatory reflex (including inhibition of macrophage/inflammatory cell cytokine generation via $\alpha 7$ nicotinic receptors - $\alpha 7$). Sympathetic activity also directly impacts the heart while influencing cytokine/substance P release from inflammatory cells, B cell antibody production, and acetylcholine (ACh) release from choline acetyl-transferase expressing T cells. Cytokines/inflammation in turn signal to the central nervous system via vagal and sensory afferent fibers (not shown). Metabolic changes with altered cortisol, catecholamines, T3 and GH include insulin-resistance, hyperglycemia, lipolysis and elevated circulating free fatty acids (FFAs). Which of this array of neurohumoral, inflammatory and immune factors are key in inhibiting myocardial stress resistance remains to be established.

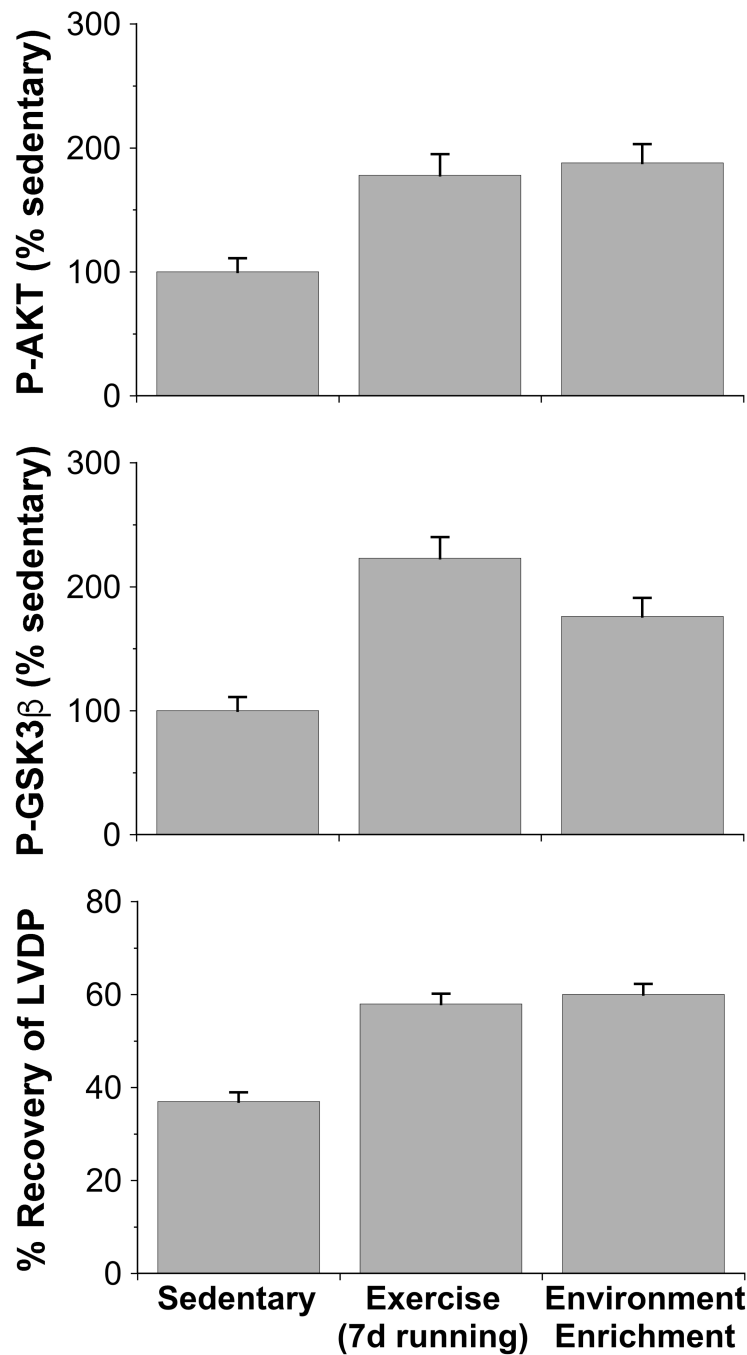


Fig. 3. Environmental enrichment may mimic the cardioprotection with physical exercise in mice. These unpublished data show effects of environment enrichment (initial placement of a locked running wheel in the cage for 2 days) compared with 7 days of voluntary wheel running in Langendorff perfused hearts isolated from these mice [54]: phospho-activation of myocardial AKT (pro-survival); phospho-inhibition of GSK3 β (pro-injury); and functional recovery from 25 min global ischemia and 45 min reperfusion (% recovery of left ventricular pressure development, LVDP). Note the similar signalling and cardioprotective outcomes with both active wheel-running and simple environment enrichment. Data are means \pm SEM ($n=6-7$).